Information Technology

Theorie chemischer Organisationen angewendet auf Infektionsmodelle

Chemical Organization Theory Applied to Virus Dynamics

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Abstract

Chemical organization theory has been proposed to provide a new perspective to study complex dynamical reaction networks. It decomposes a reaction network into overlapping sub-networks called organizations. An organization is an algebraically closed and self-maintaining set of molecular species. The set of organizations form a hierarchical "organizational structure", which is here a lattice. In order to evaluate the usefulness of this approach we apply the theory to five models of immune response to HIV infection. We found four different lattices of organizations, which can be used as a first classification of the models. Furthermore, each organization found can be assigned to a functional state of the system. And finally, the lattice of organizations can be used to explain a treatment strategy on a more abstract level, i.e. as a movement from one organization into another.

Zusammenfassung

Die Theorie chemischer Organisationen eröffnet einen neuen Weg um komplexe dynamische Reaktionsnetzwerke zu analysieren. Dazu wird das Netzwerk in überlappende Teile, Organisationen genannt, zerlegt. Eine Organisation ist eine bezüglich der Reaktionsregeln algebraisch abgeschlossene und selbsterhaltende Menge molekularer Spezies. Die Menge aller Organisationen eines Systems bildet eine hierarische "Organisationsstruktur". Um die Nützlichkeit diese Ansatzes zu bewerten, haben wir fünf Modelle der Immunantwort bei HIV-Infektion untersucht. Dabei haben wir vier verschiedene Organisationsstrukturen gefunden, die zur Klassifikation der Modelle und ihrem potenziellen Verhalten verwendet werden können. Jeder gefundenen Organisation konnte ein Systemzustand zugeordnet werden. Ferner kann die Organisationsstruktur dazu verwendet werden, eine Medikationsstrategie auf einer abstrakteren Ebene zu erklären, nämlich als Bewegung von einer Organisation in eine andere.

1 Introduction

Biochemical reaction networks in living cells are highly interconnected. In order to tackle their complexity, network theory has been successfully applied in their analysis [2]. A systematic analysis of many biological organisms revealed design principles in metabolic networks that enhance robustness and fault-tolerance of these systems [16]. Structural features contributing towards robustness in biological systems are for example feedback loops, redundancy, and modularity [28]. Such properties are vital for living organisms as they continuously have to adapt to an ever-changing environment. Because a failure of metabolite production can be fatal, analysis of metabolic networks with respect to the minimum set of reactions necessary to maintain the production leads to an understanding of the fragility of the system [17]. Adaptive properties of biological processes are structurally supported by biochemical reaction networks [3]. Although interactions within biochemical networks also include physiological effects, conformational change, and spatial constitution (*c.f.* [8]), topological features of the reaction network have been emphasized for reliable information processing [18]. Furthermore it should be noted that natural organisms have been used as a source of inspiration for implementing artifical information processing systems [9, 10].

Precise description of the dynamical behavior of these systems requires knowledge of the kinetics and the parameters for each reaction. However, several aspects of the dynamical behavior can already be inferred from the static structural information of the reaction network [1]. Correlations between the stability of steady states and the stoichiometric matrix have been studied by Clarke [6, 7]. Under steady state assumptions, feasible flux distributions of metabolic networks are also obtained from the stoichiometry information [25, 26]; and conclusions about equilibrium states and their uniqueness can then be drawn using methods developed by Feinberg and Horn [14]. Further assuming a maximum bacterial growth rate, a metabolic network reconstructed from genome sequence data has been tested with experimental data [13]. When modelling biochemical reaction networks with petri nets [23, 24], the concepts of liveness, reachability, t-invariants, and p-invariants imply potential dynamical behaviors [19].

An advantage of these approaches is that kinetic parameters, which are scarce in biological data, are not required. The analysis method investigated in this paper and described in the next section, operates on the same level of abstraction. That is, an algebraic analysis of the reaction network explains the dynamical behavior of the system. As a demonstration of how the theory connects network structure with dynamical behavior, biochemical reaction networks underlying HIV immunology models are investigated.

2 Chemical Organization Theory

Inspired by Fontana and Buss [15], chemical organization theory has been introduced [11, 27] aiming at an understanding of dynamical complex biochemical processes just taking stoichiometry into account. An *organization* is defined as a set of molecular species that is (algebraically) closed and (dynamically) self-maintaining. The first property, *closure*, ensures that applying any reaction rule to members of an organization generates its members only; the second property, *self-maintenance*, is a theoretical capability of an organization to maintain all of its members. Those two properties, independent of the type of reaction dynamics assumed, stabilize qualitative states of a reaction vessel: Neither new molecular species appear, nor does any existing molecular species disappear. When the theory is applied, a reaction network is decomposed into overlapping sub-networks, forming a partial hierarchy of organizations. The hierarchy is used to describe the potential dynamical behavior of the reaction system as a movement between organizations. Only stoichiometric information is required to identify all organizations, making the method well suited for biological networks where kinetic data is often scarce. In contrast to other methods, no steady state assumptions are made so that dynamical behaviors of accumulating mass are also considered. Note also that using the closure property alone can already provide a powerful tool to get insight into the structure and function of a large network consisting of several thousands of compounds [12].

The organizations of the reaction networks studied in this paper form a lattice. A lattice is an algebraic structure that consists of a set of elements and two operations, union and intersection; such that given any two elements of the lattice, both their union and their intersection are elements of the lattice. A lattice can be visualized with a Hasse-diagram. Here the vertical position of an organization is determined by the number of molecules it contains. The largest organization, which always exists in a finite lattice,

can be found at the top of the Hasse-diagram. At the bottom, we can see the smallest organization. Two organizations are connected by a line if the upper organization contains all species of the lower organization and there is no other organization in between them. The Hasse-diagram represents the hierarchical organizational structure of the reaction network under study.

A theorem links the dynamics of the system with the lattice of organizations by stating that each fixed point of the dynamical system is an instance of an organization. As such the organizational study can be used to find out what possible sets of molecules might be contained in a steady state. In our example the resulting steady states where already well known, and as such the results are not surprising. Yet, as predicted, they were all instances of organizations; practically confirming the possibility to use the theory as a first analysis of a system.

3 Results

Applying chemical organization theory to chemical reaction networks reveals the organizational structure of the model. Since virus (HIV) dynamics are modeled with a set of ordinary differential equations (ODEs), translation of the models into a collection of chemical reaction rules is necessary. The results of analyzing five viral dynamics models with chemical organization theory are summarized in Table 1. The level of abstraction increases from left to right. Moving from right to left requires additional information, *e.g.*, reaction kinetics to construct an ODE model from the network model. Depending on the purpose of the model, the appropriate level must be chosen carefully. Exact quantitative analysis of the model behavior is possible with ODE models, but estimating kinetic parameters is critical as pointed out in [30].

3.1 Basic Model

The HIV infection process involves mainly three molecular species: uninfected T cells x, infected T cell y, and free virus particles v. Provided that the concentration of each species is specified by x, y, and v, respectively, the infection dynamics can be modeled as follows [21]:

$$\begin{aligned} \dot{x} &= \lambda - dx - \beta xv \\ \dot{y} &= \beta xv - ay \\ \dot{v} &= ky - uv. \end{aligned}$$

Since the deterministic ODE model is contrived on a basis of interactions between molecular species, the infection process can be represented as a form of chemical reaction network. Since uninfected T cells are produced at a constant rate λ, molecular species x is considered as an input species, resulting in the reaction rule: $\emptyset \rightarrow$ x. Each species is assumed to decay in the ODE model. As a reaction rule, each species is transformed into the empty set: $\mathsf{x} \rightarrow \emptyset$, $\mathsf{y} \rightarrow \emptyset$, and $\mathsf{v} \rightarrow \emptyset$.

The infection with HIV transforms an uninfected T cell x into an infected cell y, which is denoted by the term βxy. This interaction can be represented by the reaction rule: x+v $\rightarrow$ y+v. Since variable v is not changed by that term, virus species v is also included in the righthand side of the reaction rule. The last term to consider is ky representing the virus replication in the infected cell: $\mathsf{y} \rightarrow \mathsf{y} + \mathsf{v}$.[1]

Computing the closed and self-maintaining sets of molecular species in the HIV infection networks reveals the existence of two organizations. The smaller organization consisting of only uninfected T cell x can be interpreted as the state without virus infection. The larger organization contains all three molecular species and corresponds to the infected state. From mathematical analysis [21] it is known that the ODE model has two equilibrium states. These two states correspond to the two organizations of the network. This demonstrates that chemical organization theory delivers a proper analysis of the reaction network regarding its dynamical behavior.

3.2 CTL response

The HIV infection model is extended to include immune responses [21] by adding a new decay term for the infected T cell y:

$$\dot{y} = \beta xy - ay - pyz$$

where variable z represents the concentration of the cytotoxic T Lymphocyte (CTL) species z. The dynamics of CTL is given as:

$$\dot{z} = cyz - bz.$$

Upon detection of infected T cells y, CTL proliferates at rate cyz.

In addition to the reaction rules from the previous model, a decay reaction for CTL z and two further reactions are derived from the ODE model. The collision of infected T cell y and CTL z can have two outcomes: annihilation of infected cells ($\mathsf{y} + \mathsf{z} \rightarrow \mathsf{z}$) or proliferation of the CTL cells ($\mathsf{y} + \mathsf{z} \rightarrow \mathsf{y} + 2\mathsf{z}$). Analyzing the reaction network of nine reactions, the hierarchy of organizations contains three levels. The new species z is only involved in the largest organization. The two lower organizations are identical

[1] Since infected T cell y decays and, at the same time, produces virus v, we can simply write $\mathsf{y} \rightarrow \mathsf{v}$ instead of two reactions. With respect to the theory, it does not change the result.

with the organizations of the previous model. The top organization corresponds to the equilibrium of the ODE model in which CTL immune response is continuously activated. According to a mathematical analysis [21], the activation of the immune system may be temporal if the concentration of the infected cell is smaller than a threshold value. This equilibrium with infected cells but without immune response is contained in the middle organization. The smallest organization at the bottom of the hierarchy represents the state with no infection.

3.3 Memory CTL

An ODE model with four molecular species is constructed in [29]: uninfected $CD4^+$ T cells x, infected $CD4^+$ T cells y, CTL precursors w, and CTL effectors z. The concentration of each species is specified by x, y, w, and z, respectively. The dynamics is as follows:

$$\begin{aligned}\dot{x} &= \lambda - dx - \beta xy\\ \dot{y} &= \beta xy - ay - pyz\\ \dot{w} &= cxyw - cqyw - bw\\ \dot{z} &= cqyw - hz.\end{aligned}$$

A set of chemical reaction rules is derived from the ODE model. Since the virus species is omitted in the model, the virus infection occurs when infected cells attach to the uninfected: $\mathsf{x} + \mathsf{y} \rightarrow 2\mathsf{y}$. The CTL precursor differentiates to CTL effector on contact with virus infected T cells: $\mathsf{y} + \mathsf{w} \rightarrow \mathsf{y} + \mathsf{z}$, and the CTL effector kills infected T cells: $\mathsf{y} + \mathsf{z} \rightarrow \mathsf{z}$. In accordance with the term $cxyw$, proliferation of the CTL precursor is also dependent on both infected and uninfected T cells: $\mathsf{x}+\mathsf{y}+\mathsf{w} \rightarrow \mathsf{x} + \mathsf{y} + 2\mathsf{w}$. Despite the changes in the model, we found no major differences in the reaction network with respect to the organizational structure.

3.4 Quiescent Cell

Since the target T cell must be activated to be susceptible to infection, a model including the resting cell has been analyzed in [5] and was simplified in [4] as follows:

$$\begin{aligned}\dot{Q} &= \lambda - d_Q Q - \theta(v+B)Q\\ \dot{x} &= s\theta(v+B)Q - dx\\ &\quad -(1-\kappa)kvx\\ \dot{y} &= (1-\kappa)kvx - ay\\ \dot{v} &= ky - uv.\end{aligned}$$

Variable Q represents the concentration of quiescent cell species Q and variable B represents the concentration of any other antigen B than HIV v[2]. The quiescent cell is activated by both HIV and other antigens into an uninfected T cell at rate $\theta(v + B)$, and the activation is written in a form of reaction rules as follows: $\mathsf{Q} + \mathsf{v} \rightarrow \mathsf{x}+\mathsf{v}, \mathsf{Q}+\mathsf{B} \rightarrow \mathsf{x}+\mathsf{B}$. Additionally, the chemical reaction network derived from the ODE model is composed of the infection process by HIV ($\mathsf{x}+\mathsf{v} \rightarrow \mathsf{y}+\mathsf{v}$), virus proliferation ($\mathsf{y} \rightarrow \mathsf{y}+\mathsf{v}$), decay reactions, and an influx of Q.

Analyzing the reaction network with the theory of chemical organizations reveals four organizations. Since it is the quiescent cell which has an influx, the smallest organization is the set $\{\mathsf{Q}\}$. Directly above it, there are two distinct organizations. The one with four molecular species corresponds to the activation of the quiescent cell by HIV v and the infection of activated T cells x. Once the quiescent cell is transformed into the uninfected T cell, the HIV infects the T cell. At the same time, the infected T cell is necessary for the virus to reproduce. Thus, the infected T cell y is also part of the organization so that the species set becomes closed and self-maintaining. The other organization indicates the activation of the quiescent cell by the other antigen B. Both organizations contain the activated form of the T cell x. They only differ in the antigen responsible for the infection. The analysis using organization theory allows to distinguish between the two infection scenarios.

3.5 Drug Effect

Perelson et al. [22] developed a viral dynamics model to analyze the effects of two antiretroviral drug treatments. The reverse transcriptase inhibitor, blocking the infection with HIV, is represented in the model as coefficient $1 - \kappa$ ($0 \leq \kappa \leq 1$). High efficacy of the drug corresponds to $\kappa \approx 1$. We should note that the perfect inhibitor is represented by $\kappa = 1$, and the set $\{\mathsf{x}\}$ is the only organization although it is impractical to assume perfect inhibitions. The second antiviral drug, the protease inhibitor, impairs the protein synthesis process in the cell with efficacy η so that infected T cell y produces non-infectious virus v_{NI}: $\mathsf{y} \rightarrow \mathsf{y} + \mathsf{v}_{NI}$. When the inhibition failed with probability $1 - \eta$, the HIV reproduction reaction becomes as follows: $\mathsf{y} \rightarrow \mathsf{y} + \mathsf{v}_I$ where v_I represents normal infectious free virus.

Considering also the extreme values of drug efficacy η, there are three different networks with respect to the proliferation of HIV giving rise to three different organizational structures. In case the drug is not applied to the patient or does not have any effect ($\eta = 0$), only the infectious virus is generated. This is identical case with the HIV infection model discussed before. The

[2]The ODE model considers also drug therapy with a reverse transcriptase inhibitor, and the efficacy of the drug is represented by $0 \leq \kappa \leq 1$.

smallest organization is the set containing only uninfected T cell x, and above it, free virus particle v and infected T cell y are joined to form the organization. By setting $\eta = 1$, perfect inhibition of the infectious virus proliferation is modeled and only the non-infectious virus is produced from the infected T cell. The organization corresponding to the virus infected state is, in this case, composed of non-infectious virus v_{NI} instead of the infectious type. Statistically speaking, however, reproduction processes of both infectious and non-infectious virus are present in the dynamical reaction system, and the efficacy parameter is set to a value within $0 < \eta < 1$ to model the practical situation. If both of the reactions are included in the network simultaneously, the set containing both infectious and non-infections virus is found to be an organization.

4 Discussion

In this study we have shown that different models of immune response to HIV infection possess different lattices of organizations. As we can see in Table 1, a lattice provides a quick overview of the model's structure and its potential dynamics. We can see which kind of species together can constitute a steady state, namely exactly those forming an organization.

The difference in organizational structure (naturally) reflects the way the model has been extended. For example, changing the basic model by adding the immune response (Table 1, Row 1 and 2) results in a new organization to appear, which represents the infection antagonized by the immune response z. Extending the model does not necessarily change the lattice structure, as shown by the CTL memory model (Table 1, Row 3). The intention of the modelers is to emphasize effects of CTL memory precursor w for long-term viral load control mediated by CTL. The ODE model is designed for a steady state to contain both the CTL precursor and CTL effector z. This design principle is realized in the organizational structure as the largest organization to contain both the precursor and the effector.

The fourth model is an example for extending Model A such that the organizations are not arranged in a chain in the Hasse diagram. The main concern of the model developers is to include quiescent cells Q, but the reason of the lattice structure not being in a chain is the general antigen B in addition to HIV virus particle v. From the organizational structure, both antigens B and v appear with activated T cell x. Only v of the two antigens is associated with infected T cell y, as intended by the model design.

Through the last model (Table 1, Row 5), we demonstrate how parameters could be handled in the static reaction network analysis. The quantity of some parameters determines the reaction network structure leading to different results of the static analysis. The efficacy of protease inhibitors represented by η is our example. Infected T cell y probabilistically produces infectious virus v_I or non-infectious virus v_{NI} as shown in the reaction network model of ODE Model E. Seeing the reaction as a stochastic process, the network structure alternates between them. When analyzing such a network with chemical organization theory, three cases are considered depending on the value of η. Two of them are described as the success and the failure of the protease inhibitions represented by $\eta = 0$ and $\eta = 1$, respectively. The other case $0 < \eta < 1$ takes a probabilistic view such that both reactions (infections and non-infections virus proliferation) occur in the whole system. We obtained lattices that differ only in their species composition. The other important parameter in this model κ, the efficacy of reverse transcriptase inhibitors, affects the results of our analysis in a trivial way.

Here, we would like to show that the strategy of a drug treatment can be explained on a relatively high (*i.e.* less detailed) level of abstraction using the lattice of organizations, namely as a movement from an organization representing an ill state to an organization representing a healthy state (see Ref. [20] for details). In Figure 1 two strategies are illustrated for the model of Wodarz and Nowak [29]. The first one tries to move the system into the smallest organization $\{x\}$, where no virus is present at all. An alternative strategy may move the system into the largest organization, where the virus is present, but also an immune system response controlling the virus. There are drugs available that can bring down the virus load by several orders of magnitude. If by this procedure the virus could be completely removed, the system would move into the smallest organization, because the set $\{x, w, z\}$ is not self-maintaining and thus the system moves down into organization $\{x\}$. However, it has been observed that although the virus load can be decreased below detection limit, the virus cannot be fully removed. Hence, after stopping the treatment the virus will reappear. Therefore, the actual strategy described by Wodarz and Nowak is not to move the system into the lowest organization, but into the highest organization. In practice, this is achieved by apply-

ing the drug periodically allowing the immune defense to increase [29].

It is important to note that choosing the right level of abstraction depends on what should be explained. The lattice of organizations is a suitable level of abstraction for describing the overall strategy. However, *how* an actual drug treatment should look like in order to move the system into the largest organization cannot be answered by chemical organization theory. For this we have to chose a more detailed level of abstraction, *e.g.*, the ODE model, which provides information on how the system can move from one organization to another.

In summary we can conclude from our study that the theory of chemical organizations appears as a useful tool, which creates a first, rough map of the structure and potential dynamical behavior of a reaction system. The obtained scaffold, *i.e.* the lattice of organizations, can guide further more detailed analysis, which may study the dynamics within or in-between organizations using classical tools from dynamical systems theory. The results of more detailed studies can in turn be explained and summarized with respect to the lattice of organizations resulting in a global picture.

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Literatur

[1] J. E. Bailey. Complex biology with no parameters. *Nat. Biotechnol. 19*, 6 (2001), 503–504.

[2] A.-L. Barabási, Z. N. Oltvai. Network biology: Understanding the cell's functional organization. *Nat. Rev. Gen. 5* (2004), 101–113.

[3] N. Barkai, S. Leibler. Robustness in simple biochemical networks. *Nature 387*, 6636 (1997), 913–917.

[4] D. S. Callaway, A. S. Perelson. HIV-1 infection and low steady state viral loads. *Bull. Math. Biol. 64* (2002), 29–64.

[5] D. S. Callaway, R. M. Ribeiro, M. A. Nowak. Virus phenotype switching and disease progression in HIV-1 infection. *Proc. Biol. Sci. 266*, 1437 (1999), 2523–2530.

[6] B. L. Clarke. Theorems on chemical network stability. *The Journal of Chemical Physics 62*, 3 (1975), 773–775.

[7] B. L. Clarke. Stability of complex reaction networks. *Advances in Chemical Physics 42* (1980), 1–213.

[8] M. Conrad, K.-P. Zauner. Conformation-based computing: A rationale and a recipe. In *Molecular Computing*, T. Sienko, A. Adamatzky, N. G. Rambidi, and M. Conrad, Eds. MIT press, Cambridge, MA, 2003, pp. 1–31.

[9] P. D'haeseleer, S. Forrest, H. Helman. An immunological approach to change detection: Algorithms, analysis and implications. In *Proceedings of the 1996 IEEE Symposium on Security and Privacy* (may 1996), IEEE Computer Society Press, pp. 110–119.

[10] P. Dittrich. The bio-chemical information processing metaphor as a programming paradigm for organic computing. In *Proceedings of ARCS: Architecture of Computing Systems* (2005), LNCS, Springer, Berlin. to appear.

[11] P. Dittrich, P. Speroni di Fenizio. Chemical organization theory: towards a theory of constructive dynamical systems, 2005. arXiv:q-bio.MN/0501016.

[12] O. Ebenhöh, T. Handorf, R. Heinrich. Structural analysis of expanding metabolic networks. *Genome Informatics 15*, 1 (2004), 35–45.

[13] J. S. Edwards, B. O. Palsson. The escherichia coli mg1655 in silico metabolic genotype: Its definition, characteristics, and capabilities. *PNAS 97* (2000), 5528–5533.

[14] M. Feinberg, F. J. M. Horn. Dynamics of open chemical systems and the algebraic structure of the underlying reaction network. *Chemical Engineering Science 29* (March 1974), 775–787.

[15] W. Fontana, L. W. Buss 'The arrival of the fittest': Toward a theory of biological organization. *Bull. Math. Biol. 56* (1994), 1–64.

[16] H. Jeong, B. Tombor, R. Albert, Z. N. Oltvai, A.-L. Barabási. The large-scale organization of metabolic networks. *Nature 407* (oct 2000), 651–654.

[17] S. Klamt, E. D. Gilles. Minimal cut sets in biochemical reaction networks. *Bioinformatics 20*, 2 (2004), 226–234.

[18] K. Klemm, S. Bornholdt. Topology of biological networks and reliability of information processing, 2004.

[19] K. Lautenbach. Exact liveness conditions of a petri net class (in german). GMD Report 82, GMD, Bonn, German, 1973.

[20] N. Matsumaru, P. Speroni di Fenizio, F. Centler, P. Dittrich. A case study of chemical organization theory applied to virus dynamics. In *Systems Biology Workshop at ECAL 2005, Workshop Proceedings CD-ROM* (Kent, UK, 5-9 September 2005), J. T. Kim, Ed.

[21] M. A. Nowak, C. R. M. Bangham. Population dynamics of immune responses to persistent viruses. *Science 272*, 5258 (1996), 74–79.

[22] A. S. Perelson, A. U. Neumann, M. Markowitz, J. M. Leonard, D. D. Ho. Hiv-1 dynamics in vivo: Virion clearance rate, infected cell life-span, and viral generation time. *Science 271*, 5255 (1996), 1582–1586.

[23] C. A. Petri. *Kommunikation mit Automaten*. PhD thesis, Universität Bonn, 1962.

[24] V. N. Reddy, M. L. Mavrovouniotis, M. N. Liebman. Petri net representations in metabolic pathways. In *Proceedings of the 1st International Conference on Intelligent Systems for Molecular Biology* (1993), AAAI Press, pp. 328–336.

[25] C. H. Schilling, S. Schuster, B. O. Palsson, R. Heinrich. Metabolic pathway analysis: Basic concepts and scientific applications in the post-genomic era. *Biotechnol. Prog. 15* (1999), 296–303.

[26] S. Schuster, D. A. Fell, T. Dandekar. A general definition of metabolic pathways useful for systematic organization and analysis of complex metabolic networks. *Nat. Biotechnol. 18* (Mar. 2000), 326–332.

[27] P. Speroni Di Fenizio, P. Dittrich. Artificial chemistry's global dynamics. movement in the lattice of organisation. *The Journal of Three Dimensional Images 16*, 4 (2002), 160–163.

[28] J. Stelling, U. Sauer, Z. Szallasi, F. J. Doyle, J. Doyle. Robustness of cellular functions. *Cell 118* (2004), 675–685.

[29] D. Wodarz, M. A. Nowak. Specific therapy regimes could lead to long-term immunological control of HIV. *PNAS 96*, 25 (1999), 14464–14469.

[30] H. Wu, P. Ruan, A. A. Ding, J. L. Sullivan, K. Luzuriaga. Inappropriate model-fitting methods may lead to significant underestimates of viral decay rates in hiv dynamic studies. *J. Acquir. Immune Defic. Syndr. 21*, 5 (1999), 426–428.

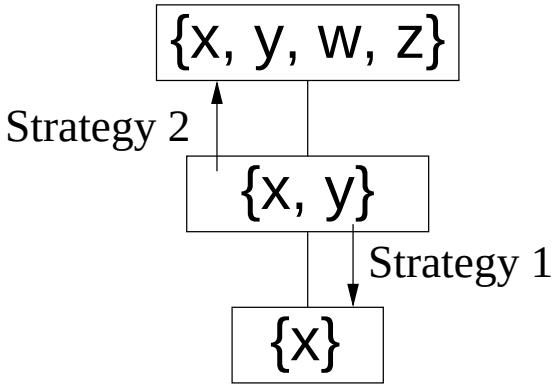
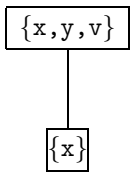
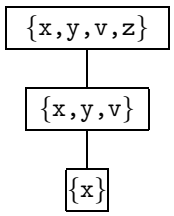
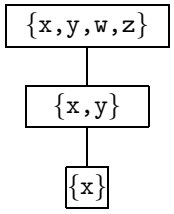
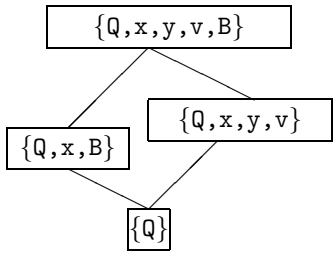


Bild 1: Illustration of two treatment strategies. Strategy 1 tries to remove HIV entirely from the system. Strategy 2 aims at establishing a long-term CTL-mediated control of viral load.

Tabelle 1: Three levels of model abstraction. The level of abstraction increases from left to right, and additional information is required to lower the abstraction level. At the highest abstraction level, we take *organizations* (sets of molecular species that are closed and self-maintaining) to understand and describe the dynamical behavior. See text for details.

ODE Model	Reaction Network Model	Organizational Structure
A: (M. A. Nowak, C. R. M. Bangham: *Science 272*, 5258 (1996), 74–79.) $\dot{x} = \lambda - dx - \beta xv$ $\dot{y} = \beta xv - ay$ $\dot{v} = ky - uv$	$\emptyset \to$ x x $\to \emptyset$ y $\to \emptyset$ v $\to \emptyset$ x + v $\to$ y + v y $\to$ y + v	
B: (M. A. Nowak, C. R. M. Bangham: *Science 272*, 5258 (1996), 74–79.) $\dot{x} = \lambda - dx - \beta xv$ $\dot{y} = \beta xv - ay - pyz$ $\dot{v} = ky - uv$ $\dot{z} = cyz - bz$	$\emptyset \to$ x x $\to \emptyset$ y $\to \emptyset$ v $\to \emptyset$ z $\to \emptyset$ x + v $\to$ y + v y + z $\to$ z y + z $\to$ y + 2 z y $\to$ y + v	
C: (D. Wodarz, M.A. Nowak: *PNAS 96*, 25 (1999), 14464–14469.) $\dot{x} = \lambda - dx - \beta xy$ $\dot{y} = \beta xy - ay - pyz$ $\dot{w} = cxyw - cqyw - bw$ $\dot{z} = cqyw - hz$	$\emptyset \to$ x x $\to \emptyset$ y $\to \emptyset$ w $\to \emptyset$ z $\to \emptyset$ x + y $\to$ 2 y y + z $\to$ z y + w $\to$ y + z x + y + w $\to$ x + y + 2 w	
D: (D. S. Callaway, A. S. Perelson: *Bull. Math. Biol. 64* (2002), 29–64.) $\dot{Q} = \xi - fQ - \theta(v+B)Q$ $\dot{x} = s\theta(v+B)Q - dx$ $-(1-\kappa)\beta xv$ $\dot{y} = (1-\kappa)\beta xv - ay$ $\dot{v} = N_T\delta y - uv$	$\emptyset \to$ Q Q $\to \emptyset$ x $\to \emptyset$ y $\to \emptyset$ v $\to \emptyset$ x + v $\to$ y + v y $\to$ y + N_Tv Q + v $\to$ sx + v Q + B $\to$ sx + B	
E: (A.S. Perelson, *et al.*: *Science 271*, 5255 (1996), 1582–1586.) $\dot{x} = \lambda - dx - (1-\kappa)kv_Ix$ $\dot{y} = (1-\kappa)kv_Ix - \delta y$ $\dot{v}_I = (1-\eta)N_T\delta x - cv_I$ $\dot{v}_{NI} = \eta N_T\delta y - cv_{NI}$	$P = 1-\eta$ $\emptyset \to$ x x $\to \emptyset$ $v_I \to \emptyset$ $v_{NI} \to \emptyset$ x + v_I $\to$ y + v_I y $\to$ y + v_I $P = \eta$ $\emptyset \to$ x x $\to \emptyset$ $v_I \to \emptyset$ $v_{NI} \to \emptyset$ x + v_I $\to$ y + v_I y $\to$ y + v_{NI}	$0 \le \kappa < 1, 0 < \eta < 1$